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Performance of bone-level implants with conical connections in the anterior maxilla: A 5-year prospective cohort study

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Abstract

Objectives: To assess clinical, radiographic and aesthetic outcomes, and satisfaction of patients treated with single implant restorations in the maxillary aesthetic region 5 years after final restoration.

Material and methods: Sixty patients (29 male/31 female, mean age 37 years) with a missing anterior tooth in the maxilla (39 central incisors/10 lateral incisors/5 cuspids/6 first premolars) received a bone-level implant with conical connection. In 29 patients, a bone augmentation procedure was necessary before implant placement (autogenous bone grafts mixed with spongiosa granules). All implants (12 with 3.3 mm diameter/ 48 with 4.1 mm diameter) were loaded after 3 months of submerged healing. The restoration consisted of an individually designed full-zirconia abutment veneered with porcelain. Follow-up with clinical and radiographic assessment was conducted until 60 months after the final restoration. Aesthetic outcome of the restoration was determined with the Pink Esthetic Score–White Esthetic Score (PES-WES). Patient satisfaction was assessed with a VAS scale and satisfaction questionnaire.

Results: Fifty patients completed the 5-year follow-up. Implant survival was 100%, restoration survival 98%. Mean bone-level change was −0.13 ± 0.66 mm with a median (IQR) pocket probing depth of 2.75 [2.25; 3.25]. The mean PES and WES scores were 6.6 ± 1.7 and 7.8 ± 1.5, respectively. Patient satisfaction was high (92.1 ± 7.8 on 100 mm VAS scale). There were no differences between patients with or without a bone augmentation procedure.

Conclusion: Bone-level implants with a conical connection are a reliable treatment option in single-tooth replacements in the maxillary aesthetic zone.

KEYWORDS

aesthetic region, bone augmentation, dental implants, maxilla, single-tooth

1 | INTRODUCTION

The maxillary anterior region is an aesthetically high-demanding region. For implant restorations, optimal pre-treatment conditions, careful surgical procedures and reliable implant materials are required (Roccuzzo, Roccuzzo, Ramanuskaite, 2018). Failing or missing teeth often coincides with deficiencies of the hard and soft tissues. Depending on the severity of these deficiencies, the end result of the treatment will be more or less compromised (Sanz-Sánchez et al., 2018). To prevent such a compromised outcome, a bone augmentation procedure prior to implant placement is often needed to reconstruct the defect.

Over time there has been a shift in the use of tissue-level implants to bone-level implants. Bone-level implants can enable the practitioner to create a natural emergence profile with individually designed abutments, which is particularly useful in the aesthetic zone (Chappuis, Bornstein, Buser, Belser, 2016; Siebert, Rieder, Eggert, Wichmann, Heckmann, 2018). A satisfying treatment outcome should be durable and stay stable for many years. Stability of the peri-implant soft and hard tissues is essential for long-lasting implant success (Schwartz-Arad, Herzberg, Levin, 2005). There is evidence that an internal conical implant-abutment connection with platform-switching is efficient in maintaining stable biological aspects. The tighter conical seal between the implant and the abutment reduces bacterial leakage and thus reduces bone loss around implants compared to non-conical connections (Schmitt et al., 2014). The reviews of Gracis et al., Goiato et al. and Palacios-Garzón et al. indicated that short-term results of this connection are favourable, but longer follow-up periods are needed to confirm the results over the long term (Gracis et al., 2012; Goiato, Pellizzer, da Silva, Bonatto, Dos Santos 2015; Palacios-Garzón et al., 2018).

Five-year and ten-year results of single-tooth replacements have been published, but specific data on single bone-level implants in healed sites in the anterior maxilla with an internal conical abutment connection are limited to the studies of Palmer, Palmer, Smith (2000), Gotfredsen (2004), Pieri, Aldini, Marchetti, Corinaldesi (2013), Berberi, Sabbagh, Aboushelib, Noujeim, Salameh (2014 and Cooper et al. (2014). All authors reported high implant survival rate between 98% and 100% and marginal bone loss <0.5mm after 5 years. All the cited studies reported on the 5-year outcome of the same bone-level implant system (Astra Tech Implant System, Dentsply Implants). However, Gao et al. (2017) published a 3-year study with another type of bone-level implants (Straumann Bone Level Implant System, Institute Straumann AG). Although this study had a shorter follow-up period, the results were comparable (100% implant survival and 0.07 ± 0.48mm bone loss).

No studies with 5-year results of the latter bone-level implant system (Straumann Bone Level Implant System) have been published, and none of the published studies included a full-scale assessment of bone-level change and the effects on soft tissue, aesthetics and patient satisfaction.

Therefore, the objectives of this prospective study were to report the clinical, radiographic and aesthetic outcomes, including biological and technical complications, and satisfaction of patients treated with single bone-level implant restorations with a conical connection, with a follow-up of 5 years.

2 | MATERIAL AND METHODS

2.1 | Study design

The study was designed as a single cohort, prospective clinical case series with a follow-up of 5 years. The manuscript was organized according to the STROBE guidelines. Recruitment of patients, implant treatment and follow-up took place at the Department of Oral and Maxillofacial Surgery of the University Medical Centre Groningen (UMCG), the Netherlands. The Medical Ethical Committee of the UMCG reviewed and approved the study protocol (METC 2009.057). Written informed consent was obtained from all eligible patients before enrolment. Details of the study design and the results of the one-year follow-up were described by Santing, Raghoebar, Vissink, Den Hartog, Meijer (2013).

2.2 | Patients

Sixty patients (29 males, 31 females; mean age 37 years) matched the inclusion criteria and were enrolled in the study (Table 1). These criteria included a single-tooth diastema in the maxillary anterior region which had to be missing for at least 3 months prior to implant placement. Patients who smoked or were periodontally unhealthy (indicated by bleeding on probing combined with pockets ≥4 mm) were excluded from the study. These 60 patients had 39 missing central incisors, 10 missing lateral incisors, five missing cuspids and six missing first premolars.

TABLE 1 Characteristics of the study group at time of inclusion

Mean age ± SD in years at implant placement	36.9 ± 15.1
Sex (*n*)	
Male	29
Female	31
Implant site location (*n*)	
Central incisor	39
Lateral incisor	10
Cuspid	5
First premolar	6
Implant diameter (*n*)	
3.3 mm	12
4.0 mm	48
Implant length (*n*)	
12 mm	16
14 mm	44
Augmentation before implant placement, *n*	29

Twenty-nine patients had a large bone defect and were augmented in a separate session without placing an implant. The nature of the defects was mainly horizontal. Autogenous bone grafts for guided bone regeneration (GBR) were harvested from the retromolar ramus area and mixed with spongiosa granules (0.25–1.0 mm; Geistlich Bio-Oss, Geistlich Pharma AG). This 1:1 mixture was placed in the defect and a membrane (Geistlich Bio-Gide®, Geistlich Pharma AG) was placed to cover the augmented area. The wound was subsequently sutured with vertical and horizontal mattresses (4-0 vicryl; Johnson & Johnson Gateway) (Raghoebar, Slater, den Hartog, Meijer, Vissink, 2009; Santing, Raghoebar, Vissink, Hartog, & Meijer, 2013). The implants were placed three months thereafter (12 implants with 3.3 mm diameter and 48 implants with 4.1 mm diameter). This resulted in a population of 60 patients which could be divided in two subgroups and allowing to determine whether augmentation therapy influences the outcome compared to non-augmented sites.

2.3 | Implant placement

All patients were scheduled to receive a bone-level implant with conical connection (Straumann Bone Level Implant System, Institute Straumann AG). Individual surgical templates were provided to place the implants in the optimal position. In cases where parts of the implant shoulder remained uncovered, or where the buccal bone wall was thin (<2 mm in thickness), a local augmentation procedure was performed with autogenous bone chips collected during implant bed preparation and anorganic bovine bone (Geistlich Bio-Oss, Geistlich Pharma AG), covered with a Geistlich Bio-Gide membrane (Geistlich Pharma AG). The wound was closed with Ethilon 5–0 nylon sutures (Johnson & Johnson Gateway). All surgical interventions were performed under prophylactic antibiotics (amoxicillin 500 mg, three times daily, or clindamycin 300 mg, four times daily for 7 days in case of amoxicillin allergy), and patients were instructed to rinse with 0.2% chlorhexidine mouthrinse twice for 7 days. Implants integrated unloaded submucosally for 3 months. A removable partial denture was worn during this healing phase, but did not interfere with treated implant site.

2.4 | Prosthetic phase

After the healing phase of 3 months, the implants were uncovered and a healing cap was placed for 1 week. A titanium-based provisional crown (temporary abutment [SynOcta Titanium Post for Temporary Restorations, Institut Straumann AG]) and composite resin (Solidex, Shofu) was then made and screwed onto the implant (torqued to 35Ncm) and patients were given oral hygiene instructions. The patients received a final restoration three months later: an individually designed full-zirconia abutment, without a titanium interface, with a porcelain crown, either cemented or screwed onto the implant, depending on the position of the screw access hole. Twenty-seven restorations were cement-retained and 33 restorations were screw-retained. In case of a cemented restoration, a zirconia coping was veneered with porcelain (Emax Ceram, Ivoclar Vivadent, Liechtenstein) and cemented with glass-ionomer cement (Fuji Plus; GC Europe). In case of a screw-retained restoration, porcelain (Emax Ceram) was directly fused to the abutment. Abutment screws were torqued to 35 Ncm.

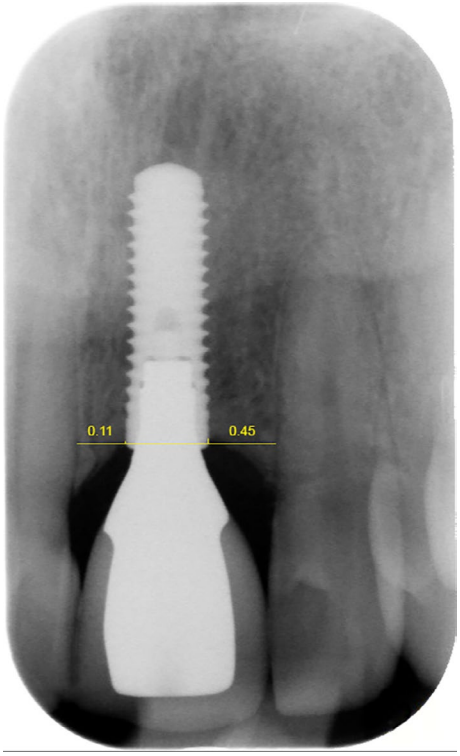

FIGURE 1 Method of measuring peri-implant bone level on an intraoral radiograph. A line was drawn from the implant shoulder to the first bone-to-implant contact on the mesial and distal side. The length of the implant body was used for calibration

2.5 | Outcome measures

Clinical, radiographic and patient-centred variables were collected before implant placement (T_0), 1 month (T_1), 1 year (T_{12}) and 5 years (T_{60}) after loading with the final restoration. Outcome measures were change in peri-implant marginal bone level, survival rate of the implant and crown, clinical variables, aesthetic outcome and patient satisfaction.

2.6 | Bone-level change

Bone-level change was recorded on standardised radiographs according to the method developed by Meijndert, Meijer, Raghoebar, Vissink (2004). Measurements were done by a trained observer with a high intra-rater reliability score (ICC 0.98 [0.96–0.98] with 95% CI). A line was drawn from the implant shoulder to the first bone-to-implant contact on the mesial and distal side (Figure 1). Mean change

was calculated with the least favourable change of the mesial and distal site to avoid an underestimation of the bone-level change. A negative value indicates bone loss.

2.7 | Survival

Survival of the implant and crown was assessed as positive when the implant or crown was present, immobile and no progressive bone loss, infection or fracture leading to removal was reported.

2.8 | Clinical variables

Clinical variables were assessed using the Modified Plaque Index (Mombelli, Van Oosten, Schurch, Land, 1987), Modified Sulcus Bleeding Index (Mombelli, Oosten, Schurch, & Land, 1987) and Papilla Index (Jemt, 1997). The pocket probing depth was measured to the nearest 1 mm using a periodontal Click-probe® with a standard pressure of 0.2–0.25N (KerrHawe Dental Corporation).

2.9 | Aesthetic outcome

Aesthetic outcome, using the modified Pink and White Esthetic Score (PES-WES) (Belser et al., 2009), was assessed by an experienced prosthodontist who was trained with the index and blinded for the applied treatment procedures.

2.10 | Peri-implant mucositis and peri-implantitis

Peri-implant mucositis and peri-implantitis were assessed according to the definition composed at the Seventh European Workshop on Periodontology (Lang & Berglundh 2011) describing peri-implant mucositis as: bleeding on probing and/or suppuration but <2 mm radiographic bone loss. Peri-implantitis was described as bleeding on probing and/or suppuration in combination with radiographic bone loss ≥2 mm.

2.11 | Patient satisfaction

Patient satisfaction was determined with a self-administered 5-point Likert-type questionnaire (Den Hartog et al., 2014) focussing on the colour and form of the crown and the colour and form of the peri-implant mucosa, ranging from very dissatisfied (score 1) to very satisfied (score 5). Specific questions were as follows:

- How satisfied are you with the form of the crown on the implant?
- How satisfied are you with the colour of the crown on the implant?
- How satisfied are you with the form of the gums around the implant?
- How satisfied are you with the colour of the gums around the implant?

Overall satisfaction was noted on a 100mm VAS-scale ranging from "very dissatisfied" at the outer left side to "very satisfied" at the outer right side.

2.12 | Statistical methods

Statistical analysis was performed to determine if there was an association between the obtained measurements. A statistical software package was used. (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. IBM Corp).

Normality of the data was checked with the Shapiro–Wilk test before determining the statistical test. Papilla Index, plaque index and bleeding index, being ordinal variables, were presented as medians and interquartile range. Pocket probing depth, being not normally distributed, was presented as median and interquartile range. Bone-level change and aesthetic evaluation, being normally distributed, were presented as means and standard deviations.

Inter-group comparison (augmented vs. not augmented) of non-parametric data (pocket depth, bone-level change, PES, WES and VAS score of patient satisfaction) was calculated using the Mann–Whitney U test. Inter-group comparison of ordinal data (Papilla Index) was analysed using the chi-squared test. The null-hypotheses were that there was no difference in bone-level change between the two subgroups. The between-time interval comparison for non-parametric continues and ordinal data were calculated using the Wilcoxon signed-rank test.

3 | RESULTS

3.1 | Patients

A total of 50 patients (23 male, 27 female) were available for evaluation after 5 years (T_{60}) of which 23 had been subjected to pre-implant reconstructive surgery. Ten patients had dropped out of the study because they either moved to another country (n = 5) or moved without leaving an address (n = 5). The assumption was made that not attending the evaluation was independent of the clinical or the radiographic condition as well as that it was independent of the patients' satisfaction. Statistical analysis was done on the evaluated 50 patients.

3.2 | Implant and crown survival

No implants were lost during the 5-year follow-up (implant survival 100%). At the time of this follow-up, 24 patients showed signs of peri-implant mucositis and one patient was diagnosed with peri-implantitis. That patient was referred for treatment when this was diagnosed

at the T_{60} follow-up. Crown survival was 98% (one crown fractured within the first year in function). In addition to this was the observation of porcelain chipping of two crowns at the T_{60} follow-up, but these patients wished no repair or replacement. During the 5-year follow-up period, no loosening of crowns and/or abutment screws was encountered.

3.3 | Peri-implant bone-level change

Primary outcome measure was peri-implant bone-level change (Table 2). Mean bone-level change at T_{60} was minor, being −0.13 ± 0.66 mm. Bone-level change was comparable between the augmented and non-augmented group (p = .53, Mann–Whitney U test, Table 3). Since the latter was based on a subgroup calculation, a post hoc group size determination was performed. It appeared that 428 participants should be needed in each group to calculate a significant difference, so it seems to be justified to mention that there is not a clinically relevant difference between the two subgroups.

TABLE 2 Mean bone-level change (mm ± *SD*) from one month after crown placement (T_1) to 5 years after crown placement (T_{60})

Mean change (n = 50)	−0.13 ± 0.66	
	n	%
Implant bone loss		
0–0.5 mm	44	88
0.6–1.0 mm	5	10
1.1–1.5 mm	0	0
1.6–2.0 mm	0	0
>2.0 mm	1	2

Note: Largest change of mesial or distal site was used. A negative value indicates bone loss.

3.4 | Clinical parameters

A summary of the clinical parameters is shown in Table 4. Plaque was hardly present at the implant restorations. Thirteen patients had probing depths ≥5mm at the implant site. Of these 13 implants, 10 showed bleeding on probing (score 1–2), but minor peri-implant bone loss (0–0.5mm). One patient showed severe bleeding on probing (score 3) and >2 mm bone loss on the peri-apical radiograph and was subsequently referred for peri-implantitis treatment. Calculations in Table 3 show a statistically significant deeper probing depth in the augmented group. The patient diagnosed with peri-implantitis belonged to the augmented group.

3.5 | Aesthetic rating and patient satisfaction

A summary of the aesthetic evaluation and the patient satisfaction score is shown in Table 5. Mean PES at T_{12} was 6.9 ± 1.8 and had not significantly decreased at T_{60} (6.6 ± 1.7, p = .30, Wilcoxon signed-rank test). Also, the WES score hardly showed changes between T_{12} and T_{60} (from 7.5 ± 1.7 to 7.8 ± 1.5, p = .21 Wilcoxon signed-rank test). Between group comparison revealed a statistically significant better PES for the non-augmented group (p = .01, Mann–Whitney U test) but no statistical significant different WES (p = .30, Mann–Whitney

TABLE 3 Difference between the subgroups augmented and non-augmented at 5 years after crown placement (T_{60})

	With pre-implant augmentation (n = 23)	Without pre-implant augmentation (n = 27)	P-value CI 95% p < .05
Bone-level change T_1–T_{60} Mean ± *SD*	−0.23 ± 0.91	−0.06 ± 0.30	p = .50†
Pocket probing depth (mm) Median, IQR	3.25 [2.50; 3.25]	2.50 [2.25; 3.00]	p = .037†
Papilla Index (median, IQR)	2.5 [2.0; 2.5]	2.5 [2.0; 2.5]	p = .24*
Patient satisfaction VAS score	92.1 ± 8.2	92.2 ± 7.6	p = .92†
Mean PES	6.0 ± 1.5	7.2 ± 1.6	p = .01‡
1 Mesial papilla	1.22 ± 0.52	1.30 ± 0.54	p = .59
2 Distal papilla	0.78 ± 0.52	1.19 ± 0.48	p = .008
3 Curvature facial mucosa	1.78 ± 0.42	1.85 ± 0.36	p = .53
4 Level of facial mucosa	1.13 ± 0.69	1.59 ± 0.57	p = .015‡
5 Root convexity/soft tissue colour and texture	1.04 ± 0.71	1.22 ± 0.80	p = .36

*Pearson chi-squared test.
†Mann–Whitney U test.
‡Statistical significant different.

TABLE 4 Clinical variables: pocket probing depth, papilla index, plaque index score and bleeding index score at 5 years after crown placement T_{60} (n = 50)

		Median, IQR
PPD at implant site		
Mesial		3.00 [2.00; 3.00]
Buccal		3.00 [2.00; 3.00]
Distal		3.00 [3.00; 4.00]
Palatinal		2.00 [2.00; 3.00]
Total of all sites		2.75 [2.25; 3.25]
Papilla index (median, IQR)		
Mesial		2.5 [2.0; 3.0]
Distal		2.0 [2.0; 3.0]
Plaque (median, IQR)		0.0 [0.0; 0.0]
Bleeding (median, IQR)		0.0 [0.0; 0.0]
	n	**%**
Bleeding score		
0	25	50
1	11	22
2	13	26
3	1	2

U test). Mean satisfaction was rated at 92.1 ± 7.8 and comparable between augmented and non-augmented subjects (p = .92, Mann–Whitney *U* test) (Table 3).

4 | DISCUSSION

Bone-level implants with conical connection presented with a good clinical performance in the maxillary anterior region and a high patients satisfaction after 5 years in function. Implant survival was 100% and crown survival 98%. Irrespective of the need for a pre-implant surgical bone augmentation procedure, the change in bone level was minor in both subgroups. The null-hypothesis that there was no difference in change of bone level between the subgroups could not be rejected. Regarding the 5-year results of solitary bone-level implants with a conical implant-abutment connection in the healed anterior maxilla, the outcomes of the studied implant type are in line with the results from other studies. The mean marginal bone-level change of the authors who conducted comparable studies all remained substantially under the 0.5 mm bone loss. (Berberi, Sabbagh, Aboushelib, Noujeim, & Salameh, 2014; Cooper et al., 2014; Gotfredsen, 2004; Palmer, Palmer, & Smith, 2000; Pieri, Aldini, Marchetti, & Corinaldesi, 2013). Although a different implant system was used in the afore-mentioned studies (Astra Tech Implant System), bone-level change reported in the present study is similar to results from the other cited studies mentioned previously.

A statistically significant difference was found between the pocket probing depths of the augmented group (3.25 [2.50; 3.25]) and the non-augmented group (2.50 [2.25; 3.00]; p = .04). A possible explanation could be that inherent to a bone augmentation procedure soft tissues heal differently on a surface of a newly applied material, being a mixture of autologous bone and a bone substitute. It must be noted, however, that the difference in probing depth is very small and not clinically relevant. The clinical parameters in our study—pocket probing depth, plaque score, bleeding score and Gingiva Index—are comparable to those reported by Cooper et al. (2014); Gotfredsen (2004) and Pieri et al. (2013).

In the present study, no incidences were associated with the implant-abutment connection. Previous studies have reported soft tissue complications associated with abutment screw loosening (Krishnan, Thomas, Sabu, 2014; Goodacre, Goodacre, Goodacre, 2018; Pjetursson et al., 2018). The absence of connection-related complications in this study suggests a strong fixation and tight seal of a conical connection. This was also appointed by Palmer et al. (2000).

TABLE 5 Aesthetic evaluation by means of PES and WES score, and patient satisfaction outcome of a questionnaire and a 0–100 VAS-scale, 5 years after crown placement (T_{60}) (n = 50)

Aesthetic evaluation				
	PES	**WES**	**PES score ≥ 6**	**WES score ≥ 6**
Total score Mean ± *SD*	6.6 ± 1.7	7.8 ± 1.5	74%	92%
Overall VAS score	73.1 ± 7.4			
Patient satisfaction				
	Colour of the crown	**Form of the crown**	**Colour of the mucosa**	**Form of the mucosa**
N of satisfied patients[a] (% satisfied of total)	46 (92.0%)	46 (92.0%)	41 (82.0%)	36 (72.0%)
Overall VAS score	92.1 ± 7.8			

[a]Measured on a 5-point scale. Scores 4 and 5 denote "satisfied" and "very satisfied," respectively, and were found acceptable.

PES and WES scored high and the level of acceptance (6 or higher) was exceeded in 74% for PES and 92% for WES. During the T_{60} assessment of the WES, the aesthetic outcome of 56% (n = 28 of 50) of the patients was assessed as poor because the incisal edge was in infraposition compared to the contra-lateral tooth. At the 1-year follow-up, only 26% (n = 16 of 60) patients got a poor judgement on this item. Having the same observer, this would imply that there was a change in position of the surrounding dentition relative to the implant crown. This change in position has been confirmed in the literature and addressed in a systematic review by Papageorgiou, Eliades, Hämmerle (2018). It is thought that eruption of teeth is most prone in adolescents and young adults and that this development decreases to a clinically insignificant proportion in the second decade of life (Fudalej, Kokich, Leroux, 2007). However, this was not supported by studies of Bernard, Schatz, Christou, Belser, Kiliaridis (2004) and Huanca Ghislanzoni, Jonasson, Giliaridis (2017) who studied continued eruption of natural teeth next to dental implants and found no correlation between age and infraposition of the implant crown. Nevertheless, clinicians need to be aware that long-term adverse effects of dental implants among natural teeth can be observed in terms of infraposition.

Patient satisfaction was rated high in our study. Patients were more satisfied with the crown than with the form of the peri-implant mucosa. This is in contrast to the augmented population described by Pieri et al. (2013), which reported equal satisfaction between the crown and the surrounding mucosa. Gotfredsen (2004) reported high patient satisfaction on crown aesthetics, but no specific data on the satisfaction of soft tissue.

The mean PES in the present study was high, with a higher score in the non-augmented group. On the contrary, Pieri et al. (2013) reported slightly higher PES scores for his population with augmented patients but had no comparison group. The additional surgical procedure in the augmented group could have negatively affected the aesthetic outcome due to scarring of the mucosa, which may underlie the lower PES score. Nevertheless, the patient satisfaction scores and professional rating in both groups remained high at the T_{60} follow-up evaluation.

A limitation of the study is that both patients needing and not needing an augmentation procedure were included in the study. A non-randomized controlled clinical trial would have been a better study design to explore a possible significant difference between the two subgroups. Another limitation of this study is that 10 patients (17% of the initial group) were lost to follow-up. Results of these patients could differ from the group which were seen for evaluation.

5 | CONCLUSION

This prospective case series showed that peri-implant tissues were healthy, marginal bone loss was minor, patient satisfaction was high and aesthetic outcome was favourable. Thus, a bone-level implant with conical connection is a reliable treatment option in single-tooth replacement in the maxillary aesthetic zone.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Dr. C.M. Meijndert involved in the concept and design of the study; analysed and interpreted data; drafted the article; and approved the final version of the manuscript. Prof. G.M. Raghoebar involved in the concept and design of the study; analysed and interpreted data; critically revised article; and approved the final version of the manuscript. Dr. H.J. Santing involved in the concept and design of the study; critically revised article; and approved the final version of the manuscript. Prof. A. Vissink involved in the concept and design of the study; analysed and interpreted data; critically revised article; and approved the final version of the manuscript. Prof. Dr. H.J.A. Meijer involved in the concept and design of the study; analysed and interpreted data; critically revised article; and approved the final version of the manuscript. All authors are accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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